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09/155,590	09/30/1998	JEFFREY SCHLOM	2026-4230US1	8846

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ART UNIT	PAPER NUMBER
1644	35

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/155,590	Applicant(s) Schlom et al.
	Examiner G.R. Ewoldt, Ph.D.	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *4/22/02, 9/12/02, and 2/06/03* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10-25, 27, 32-34, 66-68, and 70* is/are pending in the application.

4a) Of the above, claim(s) *16-24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-15, 25, 27, 32-34, 66-68, and 70* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. The amendments and remarks, filed 4/22/02 and 2/06/03, have been entered.

2. Claims 10-15, 25, 27, 32-34, 66-68, and 70 are being acted upon.

3. The disclosure remains objected to because of the following informalities: the instant application, filed 9/30/98, claims priority to U.S. Application No. 08/635,344, filed 4/19/96. The first line of the specification must be amended accordingly. Additionally, the first line of the specification must be amended to include the claim to priority of PCT/US97/06470, filed 4/17/97.

4. In view of Applicant's amendment, filed 2/06/03, the previous rejection under the second paragraph of 35 U.S.C. 112 has been withdrawn.

5. In view of Applicant's remarks, filed 4/22/02, the priority date of the instant claims, as they read on the elected species, the peptide comprising YLVVVGADGV, has been granted the benefit of priority of parent application 08/635,344, filing date 4/19/96.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 10-15, 27, and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. or U.S. Patent No. 5,861,372 (1999), for the reasons of record as set forth in Papers No. 16 and 23, mailed 10/11/01 and 1/14/02, respectively.

Applicant's arguments, filed 4/22/02, have been fully considered but they are not persuasive. Applicant argues "The Van Elsas et al. reference provides no motivation for one in the art to use the KLVVVGADGV (5-14,12Asp *ras*) peptide. In fact, the Van Elsas et al. reference acts to discourage the use of the KLVVVGADGV (5-14, 12Asp *ras*) peptide." Applicant bases the assertion on the fact that a different peptide, CLLDILDTAGL, bound HLA-A better than did KLVVVGADGV, and was thus, used in additional experiments.

It is the Examiner's position that, while the authors used the CLLDILDTAGL peptide in the bulk of their experiments, this usage cannot be said to teach away from the use of the KLVVVGADGV peptide. As set forth in the Introduction, the authors were attempting "to distinguish new epitopes in mutated *ras* proteins that may serve as targets for tumor-specific CTL." The fact that they began their efforts with any particular peptide does not actually teach that the other peptides set forth in Table I cannot or should not be used. Indeed, when combined with the Ruppert et al. reference, which teaches methods of increasing the binding of peptides to HLA-A2 by adding an N-terminus tyrosine (thus, resulting in the claimed peptide), the *combined* references result in the teaching of the claimed peptide and motivation for producing it. Accordingly, Applicant's legal tome regarding references that teach away from the claimed invention are irrelevant as the combined references do not teach away from the peptide of the instant claims.

Applicant argues "the Gjertsen et al. reference provides no motivation to use the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide. In reality, the Gjertsen et al. reference acts to discourage persons in the art from using the KLVVVGADGVGKSALTI (5-21, 12Asp *ras*) peptide." Applicant then points out that some patients were non-responders while one patient developed a non-specific response. Applicant follows with an additional argument regarding references that teach away from a claimed invention.

It is the Examiner's position that the reference discloses in Table II that 3 out of 5 patients displayed the mutation found in the peptide of the instant claims. Accordingly, this provides motivation enough for the use of peptides with the 12Asp mutation. The fact that the authors did not have complete success in the preliminary experiments cannot be said to "discourage" the use of the claimed peptide. In fact, the reference points out that "Three patients with NC in tumour mass, with tumour-related pain, noticed pain relief. The 2 patients

with immune response against the immunising peptide experienced enhanced quality of life" (page 451, column 2). Applicant's assertion regarding discouraging results would seem to be in error given the facts: all 3 non-responders "noticed pain relief" and both responders "experienced enhanced quality of life". Accordingly, the experiments must be considered to be highly successful given the positive results and the difficulty in treating incurable pancreatic cancer. Again, Applicant's legal arguments regarding references that teach away from a claimed invention must be considered irrelevant given the actual teachings of the reference in question.

Applicant argues "It is respectfully asserted that the Ruppert et al. reference provides no motivation to create Applicants' exact sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). For a 10-mer peptide, Ruppert et al. use four possible amino acids at position 1 (A, Y, F, and W), and eight possible amino acids at position 8 (M, I, V, L, W, F, and Y; see above)."

It is the Examiner's position that the reference teaches that an N-terminus tyrosine can increase HLA-A2 binding. Accordingly, the reference, in *combination* with Van Elsas et al. or Gjertsen et al. teaches the peptide of the instant claims.

Applicant further argues that "Applicants' results regarding the YLVVVGADGV (5-14, 1Tyr- 12Asp *ras*) peptide are surprising and unexpected in view of the results of Ruppert et al. Ruppert et al. indicate that, for 10-mer peptides, D is contraindicated at position 8."

It is the Examiner's position that Figure 3 of the reference indicates that an Asp at position 8 would have just a minimal negative effect on HLA binding, but even if it had a major effect, this effect would only provide additional motivation to substitute an N-terminus tyrosine as compensation. As noted in the Gjertsen et al. reference, the mutation referred to by Applicant as 12Asp *ras* was by far the most common mutation in the patients studied, thus, this mutation was necessarily present in the therapeutic peptides and not subject to changing in attempts to improve HLA binding. Accordingly, it would have been obvious to try to overcome its' possible deleterious binding effects by adding residues (such as an N-terminus tyrosine) to compensate. Regarding Applicant's assertion of "surprising and unexpected" results, it is unclear just what results disclosed in the specification might be considered to be "surprising and unexpected". The specification merely discloses that the claimed

peptide could induce *in vitro* CTL activity. This disclosure falls far short of Gjertsen et al. showing of actual *in vivo* efficacy in which all patients received at least some benefit. Accordingly, these minimal *in vitro* results are not considered surprising or unexpected given the teachings of the prior art. Thus, Applicant's arguments regarding unexpected and surprising results are irrelevant.

Applicant argues that the '372 patent provides no motivation to create Applicants' sequence YLVVVGADGV (5-14, 1Tyr-12Asp *ras*). In fact, the '372 patent leads those in the art away from Applicants' invention. First, the '372 patent reports angiostatin and angiostatin peptides. Angiostatin shares no significant sequence homology with the ras peptides of Applicants' invention."

It is the Examiner's position that the reference merely adds an additional motivation for providing a tyrosine to a peptide, i.e., to facilitate labeling. Applicant's attempts to make more of the reference than the Examiner set forth in the rejection do not render the peptide of the instant claims patentably distinct.

Applicant argues that "the reports of Van Elsas et al. and Ruppert et al. are in conflict." In particular Applicant argues that the YLVVVGADGV peptide might have been predicted by Ruppert et al. to bind HLA better than it actually did whereas the CLLDILDTAGL peptide might have been predicted by Ruppert et al. to bind HLA less well than it actually did.

It is the Examiner's position that these types of findings indicate the inexactness of predicting specific HLA binding. Thus, one of skill in the art is left with trying the addition of mutations to peptides that might increase the probability of HLA binding, such as the addition of an N-terminus tyrosine as taught by Ruppert et al. to the peptide of Van Elsas et al.

Applicant applies the same argument to the combination of the Gjertsen et al. and Ruppert et al.

The Examiner's argument is the same as for the combination of Van Elsas et al. and Ruppert et al., i.e., one of skill in the art is left with trying the addition of mutations to peptides that might increase the probability of HLA binding, such as the addition of an N-terminus tyrosine as taught by Ruppert et al. to the peptide of Gjertsen et al.

It is the Examiner's position then that in view of the arguments above, the combination of the references render the peptide of the instant claims obvious, and that the minimal *in vitro* results achieved with said peptide cannot be considered to be particularly surprising or unexpected. Accordingly, the rejection is maintained.

8. Claims 25 and 66-67 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27, and 32 above, and further in view of U.S. Patent No. 6,039,948 (2000), for the reasons of record as set forth in Papers No. 16 and 23, mailed 10/11/01 and 1/14/02, respectively.

Applicant's arguments, filed 4/22/02, have been fully considered but they are not persuasive. Applicant argues that "the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention." Accordingly, the rejection must be withdrawn.

See the Examiner's arguments regarding the aforementioned assertions in Section 7, above.

9. Claims 33, 68 and 70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. or U.S. Patent No. 5,861,372 (1999) as applied to claims 10-15, 27, and 32 above, and further in view of U.S. Patent No. 5,800,810 (1998), for the reasons of record as set forth in Papers No. 16 and 23, mailed 10/11/01 and 1/14/02, respectively.

Applicant's arguments, filed 4/22/02, have been fully considered but they are not persuasive. Applicant argues that "the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention." Accordingly, the rejection must be withdrawn.

See the Examiner's arguments regarding the aforementioned assertions in Section 7, above.

10. Claim 34 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Van Elsas et al. (1995) or Gjertsen et al. (1996) in view of Ruppert et al. or U.S. Patent No. 5,861,372

(1999) as applied to claims 10-15, 27, and 32-33 above, and further in view of U.S. Patent No. 6,001,349 (1999), for the reasons of record as set forth in Papers No. 16 and 23, mailed 10/11/01 and 1/14/02, respectively.

Applicant's arguments, filed 4/22/02, have been fully considered but they are not persuasive. Applicant argues that "the primary references of Van Elsas et al., Gjertsen et al., Ruppert et al., and the '372 patent contradict each other and lead away from Applicants' invention." Accordingly, the rejection must be withdrawn.

See the Examiner's arguments regarding the aforementioned assertions in Section 7, above.

11. The following are new grounds for rejection.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the second word of the claim, "Pharmaceutical", should not be capitalized.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 10-15, 25, 27, 32-34, 66-68, and 70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a mutant *ras* peptide consisting of the sequence YLVVVGADGV, does not reasonably provide enablement for:

a mutant *ras* peptide comprising the sequence YLVVVGADGV,

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without

an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

The peptide of the instant claims is intended "to elicit(s) a peptide-specific human CD8+ cytotoxic T cell response" (independent Claim 10). Accordingly, the claimed peptide must be enabled for it's intended use. It is well-known in the immunological arts that for the induction of a CD8+ cytotoxic T cell (CTL) response, the peptide eliciting said response must be presented by MHC Class I (such as HLA-A2). It is equally well-known that the peptides presented by MHC Class I are severely size restricted, in particular the peptides must be of approximately 8-10 amino acids in length (see for example, Rupert et al., of record, page 929, column 1). It is also noted that this same size restriction is disclosed and confirmed in the instant specification. Only the 10 amino acid peptide of the instant claims is demonstrated to be capable of inducing any sort of CTL response (only an *in vitro* response is shown; there is no *in vivo* data). As set forth on page 38 "The influence of peptide size and relative location of residues surrounding position 12 on HLA-A2 binding were examined using a spectrum of *ras* peptides (Table 7). The 13-mer *ras*5-17(Asp12) peptide, for example, which contained the core residues for binding to HLA-A2, did not appear to bind to T2 cells." Clearly then, the specification itself discloses the limitations of HLA binding. Given this length limitation, claims reciting the term "peptide comprising", and thus subject to *no* length limitations, must be considered highly unpredictable as the vast majority of the peptides encompassed by the instant claims would not likely be enabled for their intended use. Given said unpredictability, the peptides of the instant claims must be considered to require undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, and in particular, the actual teaching of the specification that peptides encompassed by the claims cannot function for their intended use, it would take undue trials and errors to practice the claimed invention.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 at (703) 305-3014. The CM1 Fax Center telephone numbers are 703-872-9306 (before final) and 703-872-9307 (after final).

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